Attachments following last page of this Amendment:

Appendix A: Photocopy of executed Declaration and Power of Attorney as filed (1 page)

Appendix B: Photocopy of page 1 of the application as filed (1 page)

Replacement Drawing sheets (2 pages)

REMARKS

Claims 1-18 are pending in the present application. Claims 1, 2, 3, 5, 13, and 15 are amended. Support for the amended claims can be found throughout the specification and in the original claims. For example, support for the amendments to claims 3 and 13 can be found in the specification at page 3, lines 30-32, and page 10, lines 26-27. Claims 1, 2, 5 and 15 have been amended to clarify the intended scope of the invention. No new matter has been added.

The specification has been amended to address the Examiner's objections to informalities in the specification (Office Action at page 3).

Claims 1-7 and 13-15 are presently under examination, claims 8-12 and 16-18 having been withdrawn by the Examiner as drawn to nonelected inventions.

The Oath/Declaration

The Office Action states that the oath or declaration is defective because "non-initialed and/or non-dated alterations have been made to the oath or declaration". (Office Action at page 2.) Attached hereto is a copy of the declaration as filed on December 13, 2005. The declaration as filed is unmarked; the markings described by the Office appear to have been made by the Office for reasons that are not clear to Applicant. Accordingly, Applicant requests that the Examiner acknowledge that the declaration as filed was not defective in any way.

Objections to the specification

The Examiner objected to the specification because "Page 1 of the specification contains non-initialed markings." (Office Action at page 3.) Attached hereto is a copy of page 1 of the specification as filed on December 13, 2005. The specification as filed is unmarked; the markings described in the Office action appear to have been made by the Office for reasons that are not clear to Applicant. Accordingly, Applicant requests that the Examiner acknowledge that the specification as filed was not defective in any way.

The Examiner objected to the arrangement of certain items in the specification. In accordance with the Examiner's suggestion, the specification has been amended to move the

section entitled "Brief Description of the Drawings" from its original location on page 14 to a site directly following "Background of the Invention."

The Examiner also objected to the level of detail provided in the "legends for Figures 1 and 2" (apparently referring to the "Brief Description of the Drawings"). Applicant has amended the specification to include a new "Brief Description of the Drawings" section that provides the requested details, and submits replacement drawings to make the points even clearer.

As all objections have been satisfied, Applicant requests that the objections to the specification be withdrawn.

Rejections under 35 USC §112, second paragraph

Claims 1-7 and 13-15 stand rejected under 35 USC §112, second paragraph, as being indefinite because claims 1 and 2 include the phrase "screening for commonly shared light chains" (Office Action at pages 3-4). Without conceding that the claims as previously presented are indefinite, and solely for the purposes of furthering prosecution, the preambles of claims 1 and 2 have been amended to delete the allegedly indefinite language.

Claims 3 and 13 were rejected as having insufficient antecedent basis for the phrase "the antibody heavy chain is Fd" (Office Action at page 4). Claims 3 and 13 have been amended to resolve this issue.

In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-7 and 13-15 under 35 USC §112, second paragraph.

Rejections under 35 USC §103(a)

Claims 1, 2, 4-7, 14 and 15 stand rejected as unpatentably obvious over Carter (J. Immunol. Methods 248:7-15 (2001)) in view of Winter et al. (US2004/0219643). According to the Office Action at page 6,

> Carter discloses in general that in order to limit the occurrence of the formation of incorrect combinations of pairs of heavy chains and light chains so that efficient production can be achieved when producing bispecific antibodies having two different

> heavy chains, a common light chain is used that can be combined with either of the two heavy chains. Moreover, when selecting the common light chain, a search is performed for an antibody having a light chain comprising an amino acid sequence that is identical to or similar to both the groups of antibodies having one of two heavy chains and the groups of antibodies having the other heavy chain, the light chain of the antibody is used as the light chain. Carter discloses using a common light chain that can be combined with either of two heavy chains so that efficient production of bispecific antibodies can be achieved. Carter does not disclose a screening method where host cells secrete a heavy chain, a light chain is introduced into the host cell, a phage library presenting antibodies comprising heavy and light chains is prepared, and the library is selected that presents the antibodies having heavy chains uniquely bonding with different desired antigens, which is used when performing this multi-step screening.

The Examiner then goes on to opine that Winter rectifies the deficiencies in Carter, stating:

> Winter discloses methods for producing dual-specific IgG antibodies having two VH/VL pairs, one pair on each arm of the antibody where the method involves a) selecting a first variable domain by its ability to bind to a first epitope expressed from a phage display library, b) selecting a second variable region by its ability to bind to a second epitope expressed from a phage display library, c) combining the variable regions into a construct for expression by the same host; and d) selecting the dual-specific ligand by its ability to bind to said first and second epitopes expressed from a phage display library.

Applicant traverses this rejection. As discussed below, the Office has failed to establish any of the three elements necessary to support a *prima facie* case of obviousness: (1) all claim limitations are found in one or more prior art references; (2) a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention; and (3) the skilled artisan would have had a reasonable expectation of success in doing so. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 at1361 (Fed. Cir. 2007).

Applicant first addresses the first element of the three-part test: the requirement that all claim limitations be found in the cited art.

Amended claim 1 has five steps:

> (a) providing a host secreting the heavy chain of an antibody that binds to a desired antigen;

(b) introducing an antibody light chain library into the host of step (a) to cause secretion of phage libraries presenting antibodies composed of the heavy chain and the light chains;

(c) selecting a phage library that displays antibodies that bind specifically to the desired antigen of step (a);

(d) introducing the phage library selected in step (c) into a host secreting the heavy chain of an antibody that binds to a desired antigen different from the antigen of step (a) to cause secretion of phage libraries presenting antibodies composed of the heavy chains and light chains; and

(e) selecting a phage library that displays antibodies that bind specifically to the desired antigen of step (d).

Claim 2, the only other independent claim, is similar to claim 1 except with respect to the description of the second heavy chain in step (d). In claim 1(d), the second heavy chain is defined as binding to a desired antigen different from the antigen of step (a), while in claim 2(d), the second heavy chain is defined as comprising an amino acid sequence different from that of the heavy chain of step (a). The obviousness arguments presented in the Office action do not distinguish between these two claims. Below, Applicant addresses the issues with respect to claim 1, but note that the same arguments apply to claim 2 and all claims that depend from either claim1 or 2.

As essentially acknowledged in the above-quoted text from page 6 of the Office action, Carter does not disclose a screening method utilizing two hosts, each secreting an antibody heavy chain (see steps (a) and (d) of claim 1), where an antibody light chain phage library is introduced into the hosts (see steps (b) and (d) of claim 1).[1] In fact, Carter at page 10, col.2, lines 10-14, teaches pretty much the opposite approach, saying that one should start with "phage libraries that have vast H chain repertoires and a unique [] or very few [] different L chains" and

[1] Note that the respective hosts of steps (a) and (d) secrete the respective heavy chains, so must encode the heavy chains in a form other than in a phage display format.

screen such a library for antibodies that bind to each of the two desired antigens.[2] Accordingly, Carter does not teach introducing an antibody light chain library into a host that secretes a particular heavy chain, as required by steps (b) and (d) of claim 1.

Winter also taught an approach entirely different from the claimed method. Winter sought to solve the problem of "chain imbalance" inherent in typical bispecific antibodies (*i.e.*, ones assembled from two different H chains, one of which binds antigen A (here termed the HA chain) and the other of which binds antigen B (here termed the HB chain) and two different L chains, one of which (the LA chain) interacts with HA to bind antigen A and the other of which (the LB chain) interacts with HB to bind antigen B). Such a bispecific antibody would have one and only one copy of each of HA, HB, LA, and LB. "Chain imbalance" occurs when HA, HB, LA and LB don't assemble in the perfect 1:1:1:1 ratio, but instead in any of the nine other possible configurations (*e.g.*, 1:1:2:0 or 1:1:0:2 or 2:0:1:1, etc.). As described in Example 1 of this reference, Winter solved this problem by starting with two different phage libraries: the first being a phage library expressing a large variety of VH domains (VH being the variable domain of an H chain) linked to a single "dummy" VL domain (VL being the variable domain of an L chain), and a second phage library expressing the inverse: a large variety of VL domains linked to a single "dummy" VH domain. Winter screened the first library for VH domains that could bind a first antigen and screened the second library for VL domains that could bind a second antigen, selecting 24 clones from each library. DNAs encoding those selected VH domains were ligated to DNAs encoding the selected VL domains to form a new library of single chain Fv molecules. Winter then screened the new library, selecting for an scFv that could bind to BOTH the first and the second antigen. The selected scFv contained a VH that bound the first antigen and a VL that bound the second antigen, so was bispecific without having a "chain imbalance" problem. Winter also converted the scFv into an Fab format (see Examples 7 and 8). By

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[2] Carter screened this phage library to isolate a first antibody that binds to a first antigen (hereinafter "antigen A") and a second antibody that binds to a second antigen (hereinafter, "antigen B"). Carter found that, in many cases, both antibodies derived from this phage library used the same L chain and owed their differing antigen specificity solely to their H chains (hereinafter "HA chain" and "HB chain") (page 10, col.2, lines 14-24). Creating a heterodimer of an HA chain and an HB chain, each paired with an identical L chain, results in Carter's bispecific antibody having two identical L chains and two different H chains.

ensuring that the assembled antibodies contain only one type of H chain and one type of L chain, Winter was purportedly able to achieve dual specificity without the "chain imbalance" problem.

Like Carter, Winter does not teach introducing an antibody light chain library into a host that secretes a particular heavy chain, as step that is carried out twice in claim 1 using two different hosts (steps (b) and (d)). Unlike the claim 1 method, Winter's method does not even identify the desired heavy chain until the final selection from Winter's third library of scFv generated from 24 selected VH domains and 24 selected VL domains, at which point the desired heavy chain is selected at the same time as the desired light chain (combined in a scFv). Therefore, several limitations of claim 1 are not present in either of the prior art references cited by the Examiner, and the rejection fails on the first prong of the test.

Nor is the second prong of the test, the "motivation" prong, satisfied in the present rejection. The Office action at page 8 describes Winter as disclosing "combining selected binding pairs with other selected binding pairs in the same host to express bispecific antibodies sharing the same or common light chain or VL domain." The Office action does not explain where in Winter this disclosure occurs, and applicant does not see it. To the contrary, Winter discloses quite a different approach than the one attributed to it by the Office. As elaborated above in the description of Winter's technology, Winter sought to identify a single VH/VL pair that could bind to two different antigens by virtue of the VH having one antigen specificity and the VL having another. Winter did not achieve bispecificity by using two different VH domains (or heavy chains) and a common VL domain (or light chain). Rather, he sought to make, and did make, a bispecific scFv containing a single VH domain paired with a single VL domain. Winter was attempting to solve the "chain imbalance" problem by utilizing only one VH and one VL domain. Using two different heavy chains in a single antibody, the approach taken in the presently claimed method, would only exacerbate, not solve, the "chain imbalance" problem. Therefore, if anything Winter taught away from the presently claimed invention. He certainly did not provide the motivation to make it.

Unlike Winter, Carter did describe a bispecific antibody containing two different H chains and two identical L chains. However, Carter did not describe a method for producing

such an antibody that would permit one to start with two previously-identified H chains (each having specificity for a different antigen), as required by the present claims. According to Carter, one should start not with two hosts, each secreting a single, identified H chain specific for a different antigen, but rather with a library expressing many H chains and a few L chains. According to Carter's method, one then screens that library to find an H/L combination that can bind to one of the desired antigens and a second H/L combination that can bind the other antigen, sequences the light chain of each combination to see if they are identical, and if they are, combine them into a bispecific antibody containing the two different heavy chains and two copies of the identical light chain. Nothing in Carter motivates one of skill in the art to take the opposite approach required by the present claims. In fact, given that Carter's bispecific antibodies contain two different heavy chains and so would inherently suffer from the "chain imbalance" problem that Winter sought to solve, Winter taught away from pursuing any method that merely results in another Carter-like bispecific antibody.

According to the Office action at pages 7-8, Carter discloses that "the solution lies in creating binding contacts for the first antigen or epitope in one variable domain, and binding contacts for the second antigen or epitope in another variable domain, where the domains are selected so that they are mutually complementary." Applicant does not see this disclosure in Carter and asks the Office to point out where it occurs. Regardless, even if one assumes that Carter did indeed suggest such a solution, that would have led one of ordinary skill in the art to use Winter's approach, not Applicant's. As explained in detail above, Winter disclosed a method for identifying a VH that has binding contacts for a first antigen and a VL that has binding contacts for a second antigen when the VH and VL are combined in a scFv. Applicant's method is not designed to produce that sort of antibody. Thus the "motivation" attributed by the Office to Carter would actually result in Winter's VH/VL combination, not Applicant's antibody. Applicant can see no motivation in either reference to carry out the presently claimed methods, and the Examiner has not cited any other possible motivation outside of these references.

The U.S. Supreme Court has very recently ruled that the "motivation to combine" part of the obviousness test must have been apparent to one of ordinary skill in the art at the time the

invention was made and must be made explicit by the fact finder (here, the Examiner). *KSR v. Teleflex*, 550 U.S. _____ (2007). In the present case, the Examiner has cited as "motivation" supposed teachings that not only reflect a misapprehension of what the art teaches, but also would not even result in applicant's invention. Further, the KSR decision affirmed that *prima facie* obviousness can be rebutted by a teaching away in the art. Such a teaching-away can be found in Winter, as discussed above. Thus, the rejection also fails to meet the second criterion for any *prima facie* obviousness rejection.

The third prong of any *prima facie* obviousness rejection is expectation of success. The Office action at page 8 addresses this prong as follows:

> One would have been assured of success in producing the instant claimed method because methods for screening for antigen binding specificity for one group by performing searches or screening, and then performing a second search from the first selected antibody to identify antigen binding specificity for a different antigen of the second group was within the ordinary skill of the artisan and taught by Carter.

The quoted text reflects a possible misunderstanding of the presently claimed method. Applicant's claims do not describe a method that involves "performing a second search from the first selected antibody" (suggesting the Examiner believes that the second search is based on a library including the first selected antibody, as taught by Carter). Rather, the second search, *i.e.*, that laid out in step (d) of claim 1, is performed utilizing a host secreting the second heavy chain (*i.e.*, not the first heavy chain) and expressing a library of light chains, so is different from the host used in the first search (*i.e.*, that of step (b)). Carter teaches a method that involves using not a host secreting a particular heavy chain, but rather a host containing a phage library expressing many heavy chains and one or a few light chains, in order to select a first heavy/light chain combination that binds a first antigen. Carter then re-screens the same library containing many heavy chains and one or a few light chains in order to select a second heavy/light chain combination that binds a second antigen. Carter thus exploited the diversity of a heavy chain library having little or no diversity in light chains in order to identify bispecific antibodies with a common light chain, while applicant took the fundamentally different (indeed, opposite) approach of exploiting the diversity solely of a light chain library, the two heavy chains being

determined from the start. Thus, the fact that Carter was successful using Carter's approach says nothing whatsoever about whether the art would have expected applicant's opposite approach to work. Winter, who used a diverse VH library and separately a diverse VL library, describes yet another method that produces a product distinctly different from that of both Carter and the presently claimed methods. Winter's teachings thus are irrelevant to determining what the art would have expected using applicant's methods.

Because the Office has not made out even one of the three prongs of a *prima facie* obviousness case, much less all three, the rejection of claims 1, 2, 4-7, 14 and 15 as obvious over Carter and Winter must fail. Withdrawal of the rejection is respectfully requested.

The Office action rejects claims 1-3 and 13 as obvious over Carter and Winter as applied above, and further in view of Goldstein et al. (J. Immunol. 158:872-879 (1997)). The Office action says that Goldstein discloses a method for producing a bispecific fusion protein containing an Fd heavy chain linked to an EGF molecule and associated with a kappa light chain from the host cell to form an Fab linked to EGF. The bispecific nature of Goldstein's fusion protein is derived from (1) the antigen-binding function of the Fab and (2) the EGF-receptor binding function of the EGF, and not from two distinct antigen binding functions as in Carter, Winter, and the present invention. As the EGF part of Goldstein's protein is essentially irrelevant to the present invention, and the Examiner has not argued otherwise, it appears that Goldstein is cited solely for its disclosure of use of Fd and Fab, two elements of claims 3 and 13.

Claims 3 and 13 depend from claims 1 and 2, respectively. Applicant has explained above why claims 1 and 2 and their dependents are not obvious in view of Carter and Winter. Goldstein does not make up for the deficiencies of Carter and Winter. Thus, claims 1-3 and 13 are nonobvious over the combination of Carter, Winter, and Goldstein for the reasons set forth above.

Applicant believes that all of the claims under examination are patentable, and allowance thereof is respectfully requested. Enclosed is a petition for extension of time and the requisite fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-148US1.

Respectfully submitted,

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APPENDIX A